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Genetic Diseases Associated with Protein Glycosylation Disorders in Mammals

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54097

1. Introduction

Protein glycosylation is an important posttranslational modification that confers both structural and functional properties to the molecules [1]. There are several types of glycosylation with various carbohydrate structures, and biosynthesis of each sugar chain, in general, is an elaborate process of addition and processing of carbohydrates in the endoplasmic reticulum (ER) and Golgi, where a number of glycosyltransferases and glycosidases are involved in these reactions. Glycoprotein degradation, on the other hand, requires many hydrolases to act on carbohydrates and involves intracellular transport of both glycosidases and their substrate glycoproteins. Collectively, enzymes that modulate glycoprotein carbohydrates during their biosynthesis and degradation are called glycoenzymes, which play critical roles in maintaining cellular structure and function. Biosynthesis of carbohydrate moieties of glycoproteins, unlike that of DNA, RNA, or proteins, is a template-independent reaction, that is, their structures are not directly encoded by genes. However, they reflect biochemical reactions catalyzed by glycoenzymes expressed in a cell. In other words, structural integrity of carbohydrates is indirectly determined by a large number of genes coding for glycoenzymes. Therefore, mutations in any of these enzymes that affect the structures and functions of glycoproteins will cause deleterious effects on cellular activities.

Glycosylation is categorized into 2 major classes on the basis of the linkage structure between a polypeptide and a carbohydrate chain, i.e., N-linked and O-linked oligosaccharides (Fig. 1). N-Linked glycans, the most extensively studied class, are the ones attached to an asparagine (Asn) residue in the Asn-X-Ser/Thr triplet sequence (X, any amino acid except proline; Ser, serine; Thr, threonine) in a polypeptide chain. Glycans that are attached to a hydroxylamino acid residue are called O-linked oligosaccharides and can be categorized into

several subclasses, according to the types of monosaccharides directly attached to the amino acid (Fig. 1). Among them, *O*-GalNAc and *O*-Xyl are the most frequently observed modifications in mucins and proteoglycans, respectively; therefore, the former oligosaccharides are also called mucin-type glycans. In addition, novel types of O-glycosylation, including *O*-Fuc and *O*-Man, were recently identified and suggested to be involved in the regulation of essential proteins, such as notch, dystroglycan, etc. [2,3]. Since these carbohydrate chains have characteristic structures and play critical roles in cellular functions, their alterations have been found to be associated with a number of inherited diseases.

In this article, diseases that are associated with altered protein glycosylation are described. Moreover, to achieve the normal cellular function, glycoenzymes involved in glycosylation processes such as synthesis, processing, and degradation must be under the proper control. Important roles of some of these enzymes are also discussed, with a focus especially on those modulating *N*-Asn-, *O*-Man-, and *O*-GalNAc-type oligosaccharides.
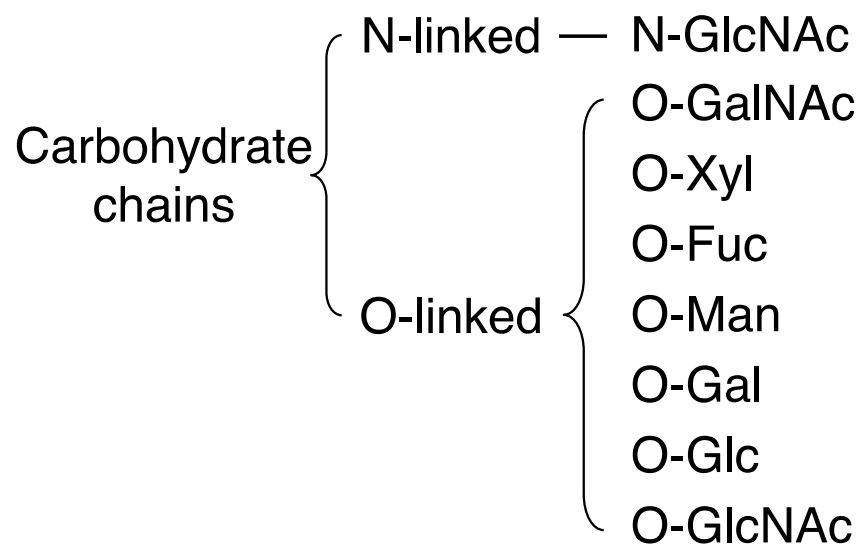

Figure 1. Classification of glycoprotein carbohydrate chains.

2. N-glycan biosynthesis

2.1. Glycoenzymes involved in N-glycan biosynthesis

N-Glycans are characterized by a linkage structure of GlcNAcβ1Asn. Its biosynthesis is distinct from that of other glycans in that a precursor oligosaccharide preassembled on a lipid dolichol (Dol) is *en block* transferred to a polypeptide chain that is being translated in the ER (Fig. 2). Consecutive addition of sugars onto dolichyl-phosphate gives rise to the final precursor product, $Glc_3Man_9GlcNAc_2$-P-P-Dol. The completed glycan is then transferred to a nascent polypeptide with an essential Asn-X-Ser/Thr sequence in the ER lumen, which is catalyzed by an oligosaccharyltransferase. Following transfer to polypeptides, N-glycans are

usually processed during intracellular transport of glycoprotein (Fig. 2). In the ER, glucosi-dases I and II remove the outermost α1,2-linked and 2 inner α1,3-linked glucose residues. The outermost α1,2-linked mannose is then released by ER α-mannosidase to generate $Man_8GlcNAc_2$-Asn. After transit to cis-Golgi, mannosidases remove 3 mannose residues, thereby producing $Man_5GlcNAc_2$-Asn, a substrate for GlcNAc-transferase I that adds a GlcNAc residue to the α1,3-linked Man. Subsequent removal of 2 mannose residues on the α1,6-linked Man occurs, and the second GlcNAc is added on the non-reducing mannose res-idues. Final addition of galactose and sialic acid residues completes biantennary complex-type N-glycans. It should be noted that additional GlcNAc-transferases can make 5 or more branched complex-type sugar chains. The branched structures in most cases are modified by consecutive addition of galactose and sialic acid residues, such that a variety of N-glycans can be generated by a series of actions of glycosidases and glycosyltransferases. Therefore, mutations of these enzymes would potentially result in production and accumulation of un-usual oligosaccharides in the cell.
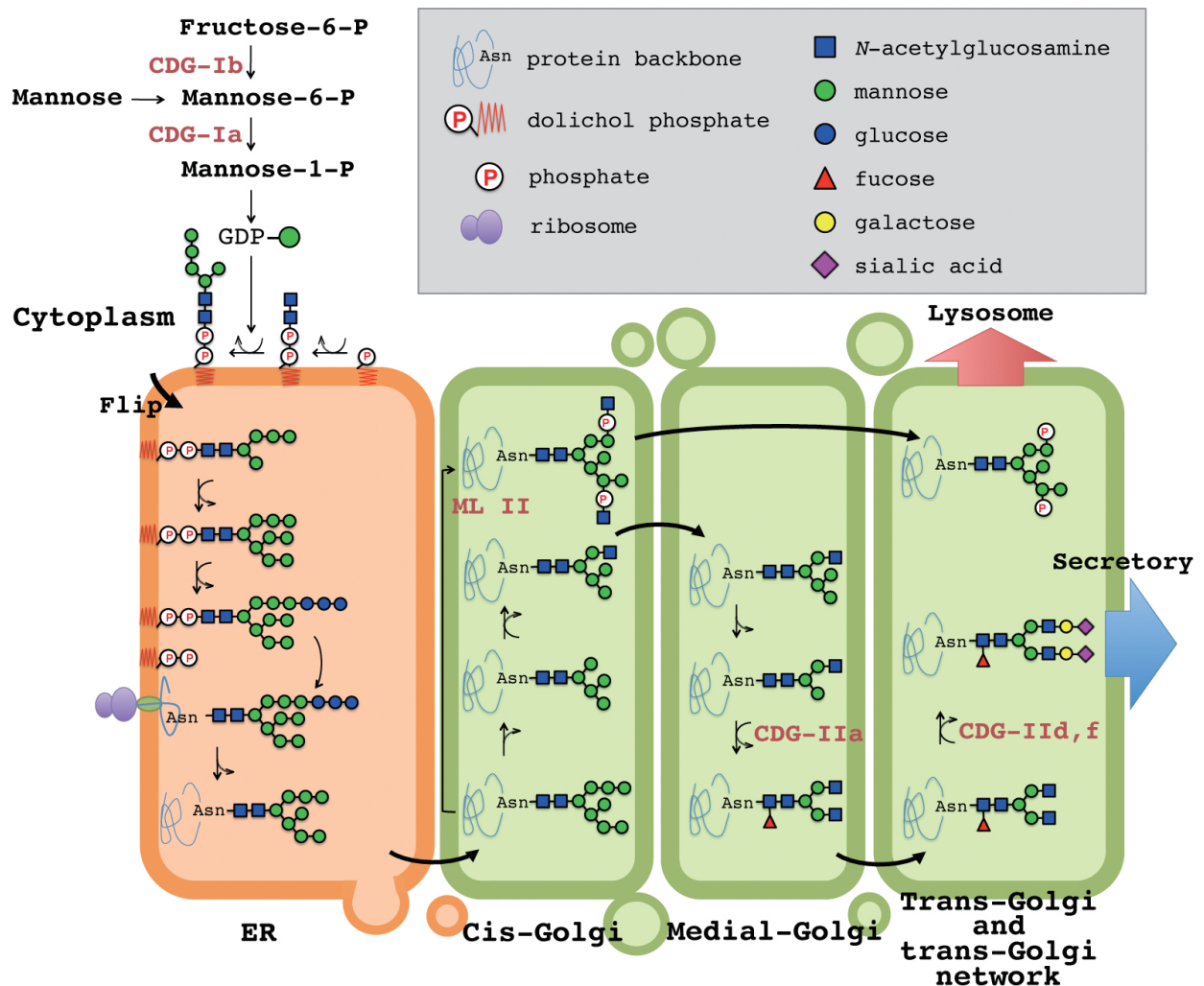

Figure 2. Biosynthesis and processing of N-linked oligosaccharides.

2.2. Disorders in N-glycan biosynthesis: CDG-I and CDG-II

Congenital disorders of glycosylation (CDG), previously known as carbohydrate-deficient glycoprotein syndrome, are a subset of genetic diseases characterized by abnormalities in glycosylation. N-Glycans are physiologically and developmentally important in various tissues, and therefore the complete absence of these oligosaccharides is lethal. Almost all CDGs are autosomal recessive; patients carrying hypomorphic mutant alleles exhibit multiple organ failure, such as neurodevelopmental disorders, hepatopathy, and immunological diseases. Since the biosynthesis of N-glycans consists of 2 distinct processes (i.e., the assembly of precursor oligosaccharides on dolichol and the processing of oligosaccharides after transfer to acceptor proteins), CDGs can be categorized into 2 general types. One type is caused by insufficient assembly of the lipid-linked precursor oligosaccharides in the ER, which is characterized by decreases in the number of N-glycans with normal structures. The other type involves defects in the processing of oligosaccharides that are transferred to proteins, thereby resulting in the production of short and simple sugar chains without affecting the number of glycans. The former type, designated as CDG-I, constitutes defects in the synthesis of dolichol lipid-linked oligosaccharide (LLO) chain as well as its transfer to proteins in the ER. The first report on CDG was made in 1980 [4], and 15 years later, it was proposed that the disease, CDG-Ia, is caused by the deficiency of an enzyme, phosphomannomutase [5]. This enzyme catalyzes the interconversion of mannose 6-phosphate and mannose 1-phosphate (Fig. 2), and its deficiency leads to a shortage of substrates (GDP-Man and Dol-P-Man) that are required for the synthesis of dolichol-oligosaccharides. CDG-Ia is the most common CDG, and its frequency has been estimated as 1 in 20,000 live births. A less common type of CDG, CDG-1b, possesses deficiency in phosphomannose isomerase (Fig. 2) [6,7]. Without this enzyme, the cells fail to convert fructose 6-phosphate to mannose 6-phosphate and, similarly to CDG-Ia, cannot generate LLOs efficiently. Interestingly, it was found that treating patients with CDG-Ib, but not CDG-Ia, with high-mannose diet alleviates the clinical manifestation, since mannose 6-phospahte can be produced by hexokinase from mannose ingested from food [7]. To date, there are several different types of CDG-I, all of which are due to genetic defects in enzymes involved in the generation of LLOs. CDG-II, on the other hand, involves malfunctions in the trimming or processing of the protein-bound chains in the ER and Golgi. For example, CDG-IIa is caused by mutations in *N*-acetylglucosaminyltransferase II (GlcNAc-TII), which adds the second GlcNAc residue to biantennary complex glycans (Fig. 2) [8]. β1,4-Galactosyltransferase, the enzyme that adds galactose after GlcNAc-TII, is mutated in CDG-IId (Fig. 2) [9]. Failure in sialylation of biantennary complex chains (Fig. 2), which results from a defect in the CMP-Sia transporter, is observed in CDG-IIf [10]. CDG-IIa, -IId, and -IIf cannot produce complex-type carbohydrates and exhibit severe phenotypes, such as mental retardation, hypotonia, and neutropenia. In addition to these examples, CDG-II patients also have diverse disorders that result from mutations in other glycosyltransferases and nucleotide sugar transporters. Moreover, there are other types of N-glycosylation disorders, including mucolipidosis II (MLII), alternatively called as I-Cell disease, caused by the lack of mannose 6-phosphate, which serve as a molecular tag to direct transport to lysosomes (Fig. 2) [11].

3. O-glycan biosynthesis

As shown in Fig. 1, there are several subclasses of O-glycosylation, and each subclass has its own biosynthetic process with specific glycosyltransferases. Disorders associated with altered *O*-Man and *O*-GalNAc glycans are described below.

3.1. Deficiency in O-mannosylation: congenital muscular dystrophies and dystroglycopathies

O-Mannosylation is related to congenital muscular dystrophies with neuronal abnormalities, such as lissencephaly and mental retardation. Muscular dystrophies are genetic diseases with degeneration and disruption of muscle fibers, resulting in the progressive wasting of skeletal muscles and atrophy. The dystrophin-glycoprotein complex (DGC) (Fig. 3) plays a critical role in maintaining muscle integrity [12,13]. It contains αDG, βDG, dystrophin, and other components, and αDG and βDG are produced from a single polypeptide called dystrophin-associated glycoprotein or dystroglycan [14] after its proteolytic cleavage. Mutations in the DGC components lead to unstable complex formation, which can be a potential cause of the diseases. In fact, dystrophin has been known to be a causative gene of Duchunne-type muscular dystrophy [15,16]. Moreover, among the DGC components, αDG is a peripheral membrane protein with a mucin-like domain, which is heavily modified with O-mannosylglycans. These sugar chains can bind to extracellular matrix proteins, such as laminin, agrin, and perlecan, through their laminin G domains [17]. The reduced αDG glycosylation was observed in a mouse model of muscular dystrophies, myd, indicating that its hypoglycosylation might be a causal factor for the disorders [18,19]. Several studies demonstrated that αDG also contains mucin-type carbohydrates, suggesting that mucin-type O-glycosylation may be involved in the proper glycosylation of αDG [20]. As described below, other mutations also cause αDG hypoglycosylation with a very wide spectrum of phenotypes [21], and all the diseases caused by the altered αDG glycosylation have been collectively designated as dystroglycanopathies [22].

O-Mannosylation, a recently appreciated glycosylation, is predominantly observed on αDG. Representative structures of O-mannosylglycans are described in the Fig. 3. The addition of a mannose residue to Ser/Thr in the α-configuration is catalyzed by an enzyme complex composed of protein *O*-mannosyltransferases, POMT1 and POMT2, in the ER [23]. GlcNAc is then transferred by a protein *O*-mannose β1,2-*N*-acetylglucosaminyltransferase, POMGnT1, in the Golgi [24]. Mutations in these enzymes result in muscular dystrophies known as Walker–Warburg syndrome (WWS) and Muscle–Eye–Brain disease [24,25]. Moreover, the disaccharide, GlcNAcβ1,2Manα1Ser/Thr, can be extended into a tetrasaccharide Siaα2,3Galβ1,4GlcNAcβ1,2Manα1Ser/Thr [26]. Occurrence of sugar chains linked to the reducing mannose residue through a phosphodiester linkage has been reported [27]. Besides POMT1, POMT2, and POMGnT1, the enzymes responsible for formation of these carbohydrates have yet to be identified. While mutations in a few genes, such as fukutin, fukutin-related protein (FKRP), and LARGE, have been suggested to cause muscular dystrophies with the αDG hypoglycosylation, their functions are still unclear, even though they possess features characteristic of glycosyltransferases [27-30]. Very recently, LARGE has been identi-

fied as a bifunctional glycosyltransferase, with both xylosyltransferase and glucuronyltransferase activities to produce repeating units of [-Xylα1,3GlcAβ1,3-], which may be added to the phosphodiester linkages (Fig. 3)[31]. Fukutin has also been reported to be related to the extended structure of αDG, which is essential for the αDG binding to its ligand laminin; however, its catalytic properties are unclear. Interestingly, while other proteins such as CD24, IgG2 light chain, tenascin R, receptor-type protein-tyrosine phosphatase, and neurofascin [32-36] are also modified with O-mannosylglycans, αDG is most likely to be the only molecule that is responsible for dystroglycanopathies [37].
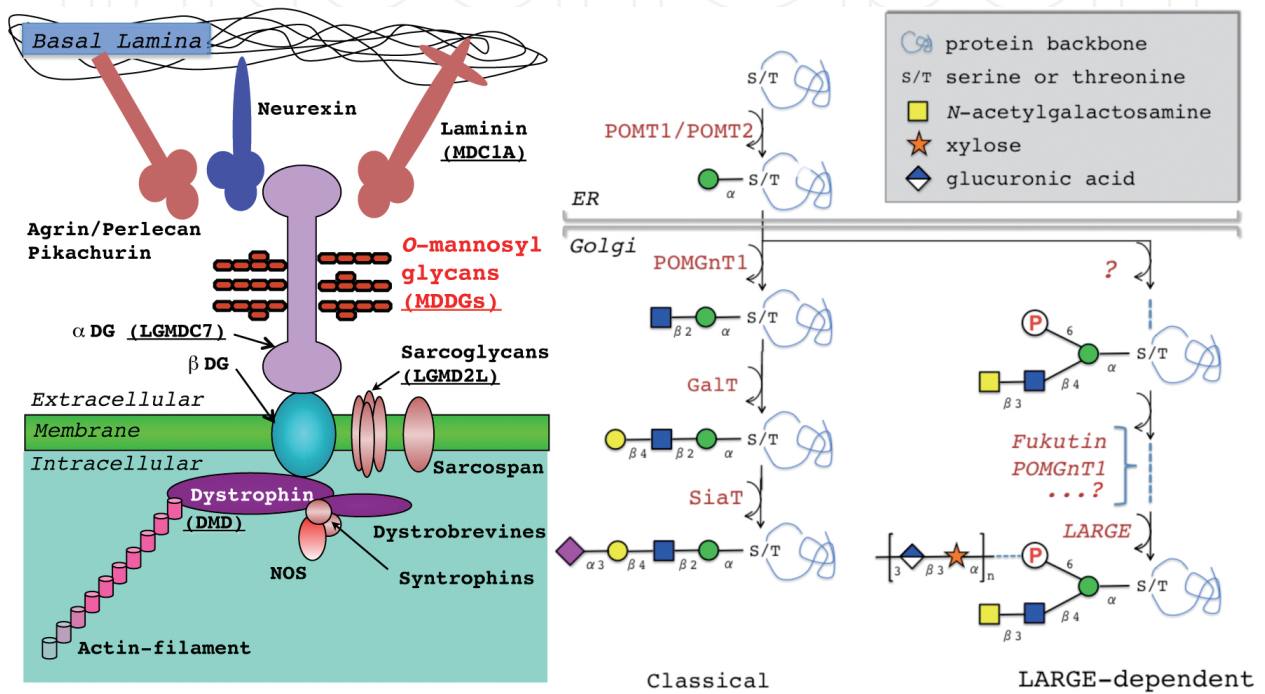

Figure 3. Dystrophin glycoprotein complex (DGC) and representative structure of O-mannosyl glycans of αDG. DGC components and disorders associated with their mutations are illustrated. MDC1A, Muscular dystrophy, congenital merosin-deficient 1A (OMIM; 607855); DMD, Duchenne muscular dystrophy (OMIM; 310200); LGMD2C, Muscular dystrophy, limb-girdle, type 2C (OMIM; 611307); LGMDC7, LGMD type C 7 (OMIM; 613818); MDDGs, Musclar dystrophy-dystroglycanopathies (see ref. [22]); NOS, nitric oxide synthase.

It is important to note that only half of congenital muscular dystrophy can be explained by gene mutations described above, suggesting that other alleles also exert effects on the phenotypes [21,22,38]. The Dol-P-mannose synthase subunit DPM3 is one candidate gene; its mutation was found in muscular dystrophy patients whose αDG glycosylation was impaired [39]. Recently, mutations in the *ISPD* gene, which encodes isoprenoid synthase domain containing, were also observed in WWS patients and are considered the second most common cause of this disorder [40,41]. While the *ISPD* function in mammals is unknown, it is involved in αDG glycosylation in zebrafish. Furthermore, a recent study suggested that glycosyltransferase-like domain containing 2, *GTDC2* or also known as *AGO61*, is a novel causative gene of WWS, based on the data from whole-exome sequencing [42], even though DG hypoglycosylation was not confirmed in patients.

3.2. Deficiency in mucin-type O-glycosylation

3.2.1. Enzymes involved in the biosynthesis of mucin-type O-glycosylation

Biosynthesis of *O*-GalNAc (mucin-type) carbohydrates begins with α-GalNAc transfer from UDP-GalNAc to a Ser/Thr residue in an acceptor polypeptide (Fig. 4). A family of UDP-Gal-NAc: polypeptide *N*-acetylgalactosaminyltransferases (GalNAc-Ts) catalyzes this reaction predominantly in the Golgi, in contrast to the initiation of other glycosylation occurring in the ER. GalNAc-Ts, the largest family members among glycosyltransferases with 20 isozymes in mammals, are cis-Golgi resident enzymes, with some of which are translocated into the ER upon signal transduction by EGF [43]. The reaction product, GalNAcα1Ser/Thr, is called the Tn-antigen and regarded as a cancer-associated carbohydrate antigen because of its accumulation in cancer cells. Moreover, distinctive core structures (cores 1, 3, 5, 6, 7, and 8) are synthesized depending on glycosyltransferases that act on the Tn-antigen, which also appears to be tissue-specific (Fig.4). Among these core structures, core 1 (Galβ1,3GalNAcα1Ser/Thr), also called the T-antigen, is the most common structure and is generated by T-synthase (C1GalT-1). This enzyme is ubiquitously expressed; however, for the proper folding and export from the ER to Golgi, it requires a specific molecular chaperone, Cosmc. Therefore, defects in either T-synthase or Cosmc would result in deficient synthesis of T-antigens. Furthermore, addition of β1,6-linked GlcNAc to cores 1 and 3 converts them into cores 2 and 4, respectively. Some of these core structures can also be extended into complex O-glycans following modifications with galactose, *N*-acetylglucosamine, fucose, and sialic acid.

3.2.2. Involvement of GalNAc-T family in genetic disorders

3.2.2.1. GalNAc-T3 as a modulator of FGF23 levels

Familial tumoral calcinosis (FTC) is a rare, autosomal recessive metabolic disorder that manifests with hyperphosphatemia and massive calcium deposits in periarticular spaces, soft tissues, and sometimes in bone. The gene underlying FTC was mapped to 2q24-q31 [44] which includes the *GALNT3* gene encoding GalNAc-T3. GalNAc-T3 protects a phosphaturic factor, FGF23, from proteolysis [45], and FGF23 inhibits the reabsorption of phosphates in proximal renal tubule. Gain-of-function mutations in the *FGF23* gene were shown to result in autosomal dominant hypophosphatemic rickets [46,47]. FGF23 secretion also requires addition of GalNAc at Thr173 in a recognition sequence motif of subtilisin-like proprotein convertases, which in turn blocks FGF23 proteolysis before its secretion. Therefore, mutations in GALNT3 would result in the cleavage of intact FGF23 and lead to FTC due to accumulation of fragmented, inactive FGF23 as well as upregulation of phosphate reabsorption.

3.2.2.2. GalNAc-T2 as a regulator of plasma lipid levels

Extensive genomic analyses recently revealed that 1q42 is associated with plasma lipid concentrations [48,49], and the *GALNT2* gene located in 1q42 was later found primarily associated
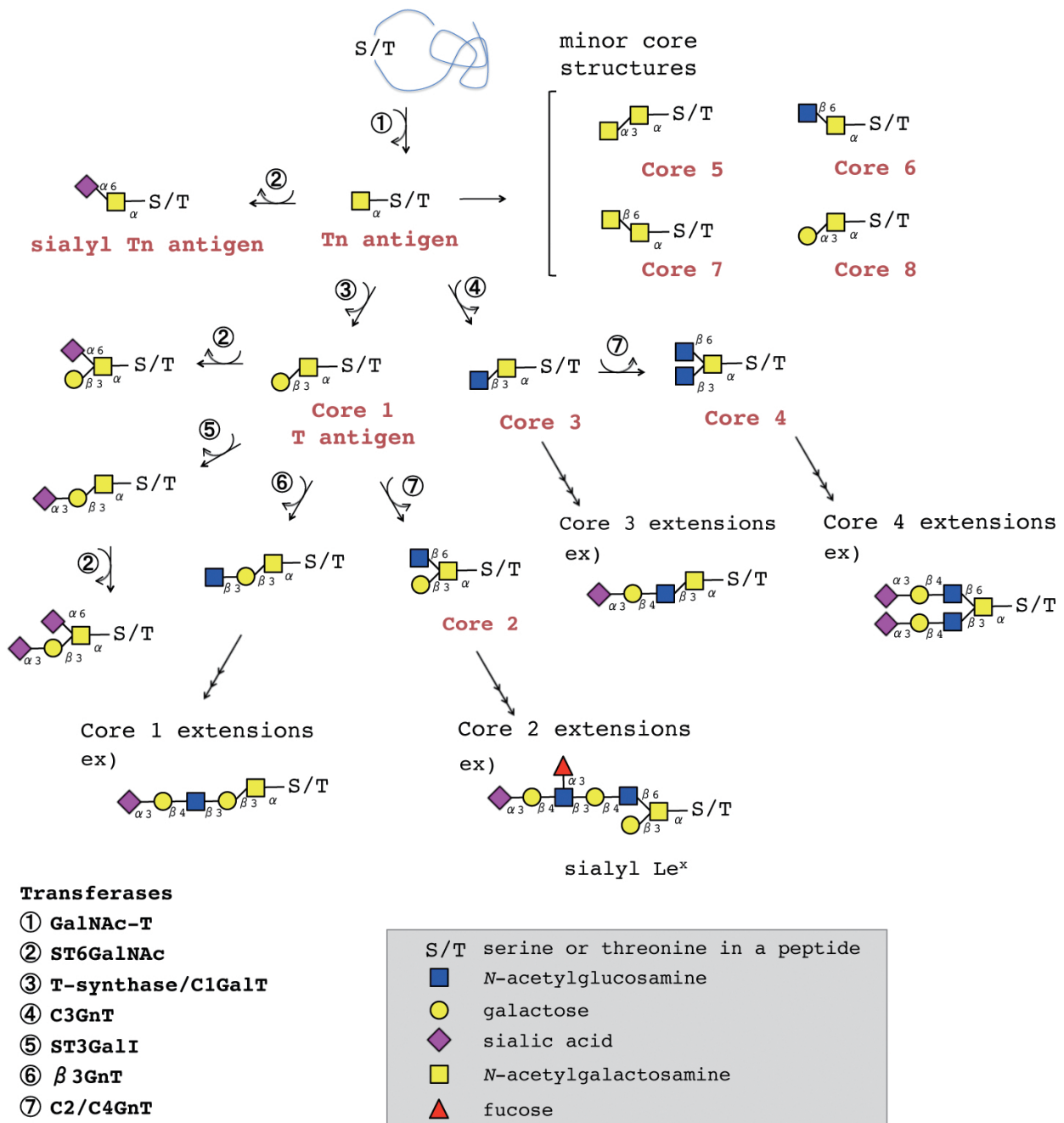
Figure 4. Biosynthetic pathway of mucin-type O-glycosylation.

with the levels of plasma high-density lipoprotein cholesterol (HDL-C). In addition, *Galnt2* overexpression in mouse liver has been shown to downregulate plasma HDL-C, and knockdown of endogenous liver *Galnt2* resulted in the opposite [50]. Moreover, apolipoprotein (apo) C-III, identified as a candidate target protein of GalNAc-T2, inhibits lipoprotein lipase (LPL), a hydrolase that degrades plasma triglycerides [51]. An apoC-III-based peptide is a substrate for GalNAc-T2 while its glycosylation by the enzyme from patient is not observed. Furthermore, neuraminidase treatment of apoC-III decreases its potential to inhibit LPL. These data suggest that GalNAc-T2 is involved in lipid metabolism via apoC-III O-glycosylation.

3.2.2.3. GalNAc-T17 as a candidate gene for Williams–Beuren syndrome and dog domestication

Williams-Beuren syndrome (WBS) is a neurodevelopmental disorder associated with physical, behavioral, and cognitive abnormalities [52] and is caused by haploinsufficiency of multiple genes at 7q11.23. GalNAc-T17, also known as WBS chromosome region 17/WBSCR17 [52], was identified in the flanking region (7q11.22) of the chromosomal deletion in WBS patients' genome. Interestingly, WBSCR17 mRNA is predominantly expressed in the nervous system [53]; therefore, haploinsufficiency of GalNAc-T17 can be expected to be related to characteristic traits of WBS patients, such as hypersociality and impairment in visuospatial processing. In addition, a recent study on the process of dog domestication reported a single SNP located near WBSCR17 in the dog genome and has implicated WBSCR17 in the early domestication of dogs [54]. It is also noted that GalNAc-T17 is a very inert isozyme, in terms of catalytic activity. GalNAc-T17, together with GalNAc-T8, -T9, and -T18, belongs to the Y subfamily, a group defined by Li *et al.* [55]. These Y isozymes contain several conservative substitutions in the catalytic domain and therefore exhibit no or extremely low catalytic activity when tested under the standard assay conditions by using synthetic mucin peptides. GalNAc-T17 in zebrafish, on the other hand, seems to be physiologically important, because its knockdown resulted in embryos that exhibited malformed brain with severe alterations in the hindbrain (ref). GalNAc-T17 has also been shown to negatively modulate macropinocytosis and lamellipodium formation in cultured cells [56].

3.2.2.4. GalNAc-Ts in other genetic diseases

Recent genome-wide studies have successively revealed novel loci associated with numerous genetic diseases. Among them, some GALNT genes have been implicated in diverse disorders or tumor susceptibility: *GALNT1*, epithelial ovarian cancer [57]; *GALNT4*, acute coronary disease [58]; *GALNT11*, congenital heart disease [59]; *GALNT12*, colon cancer [60]; *GALNT13*, sickle cell disease [61]; *GALNT14*, death-receptor mediated cancer cell death [62]; and *GALNT15*, colorectal cancer [63].

3.2.3. Tn syndrome caused by Cosmc mutations

The Tn syndrome is a rare autoimmune disease. In patients, subpopulations of all blood cell lineages carry an incompletely glycosylated membrane glycoprotein, known as the Tn antigen (GalNAcα1Ser/Thr). Since the anti-Tn antibody is present in most normal human adult sera, patients with Tn syndrome display anemia, leucopenia, and thrombocytopenia [64]. It has been suggested that the Tn syndrome is associated with somatic mutations in the *Cosmc* gene on the X chromosome. *Cosmc* encodes a molecular chaperone required for the proper folding and hence full activity of T synthase, which is responsible for adding Gal to the Tn antigen [65]. The sequence analyses of the *T synthase* and *Cosmc* genes in whole blood cells from individuals with Tn syndrome also showed that mutations were only present in the *Cosmc* gene, suggesting that these *Cosmc* mutations lead to T synthase inactivation as well as the autoimmune Tn antigen expression in blood cells of all lineages.

4. Degradation of carbohydrate units of glycoproteins

4.1. Degradation by lysosomal enzymes

Glycoconjugates, including glycoproteins, glycolipids, and proteoglycans, are biosynthesized intracellularly and incorporated extracellularly by endocytic and phagocytic mechanisms; they are transported via intracellular trafficking to lysosomes, where they are then catabolized [66]. Both N- and O-linked oligosaccharides of glycoproteins are ultimately degraded in lysosomes. Lysosomes contain more than 60 distinct acid hydrolases, so-called lysosomal enzymes, as well as their co-factors, including activators and stabilizing proteins. Most lysosomal glycosidases are classified as exo-type enzymes acting sequentially at the non-reducing termini [67] and exhibit their optimal catalytic activity under acidic pH conditions because of the function of vacuolar ATPase [68]. Some of them can also localize in non-lysosomal compartments, including early endosomes and cell membrane [69]. In addition, a group of them interact with other enzymes and activator proteins, thereby enhancing the catalytic efficiency through direct binding or presenting the substrates [70-72].

The biosynthesis of lysosomal enzymes and their co-factors is controlled by gene expression [73], posttranslational modifications, and intracellular trafficking [67,74]. Specifically, soluble matrix enzymes are N-glycosylated in the ER and phosphorylated in the Golgi apparatus at the sixth position of the terminal mannose residues (M6P), via a 2-step reaction catalyzed by Golgi-localized phosphotransferase and uncovering enzyme (*N*-acetylglucosaminidase) necessary to expose terminal M6P residues. The M6P-carrying enzymes then bind the cation-dependent mannose 6-phosphate receptor (CD-M6PR) at physiological pH in the Golgi [67,74]. The enzyme–receptor complex is subsequently transported via late endosomes (where the enzyme dissociates from the receptor at acidic pH) to lysosomes by vesicle fusion, whereas CD-M6PR, serving as a shuttle, traffics back to the Golgi apparatus. A small percentage of lysosomal enzymes are also secreted from the cell. The secreted M6P-carrying enzymes can bind to the cation-independent M6P/IGFII receptor (CI-M6PR) on the plasma membrane [67,74]. The extracellular lysosomal enzymes can then be endocytosed via glycan receptors and delivered to lysosomes, where the captured enzymes exert their normal catabolic functions. Taken together, intracellular and extracellular distributions of lysosomal enzymes are regulated by intracellular trafficking and secretion/capture system.

4.2. Lysosomal multienzyme complex for carbohydrate degradation

A group of lysosomal enzymes form a multienzyme complex to regulate their catalytic activities and turnover for efficient catabolism and stabilization. Lysosomal protective protein/cathepsin A (EC3.4.16.1; CTSA) is a multifunctional glycoprotein that exhibits not only catalytic activities but also protective functions [70,75]. CTSA is synthesized as a 452-amino-acid (54-kDa) precursor zymogen that contains intramolecular disulfide bonds and 2 N-glycans [70,75,76]. In the endosomal/lysosomal compartment, the precursor undergoes endoproteolytic processing and is converted to the enzymatically active mature form composed of 32- and 20-kDa subunits [70,75]. The mature enzyme is active at both acidic and neutral pH and functions as cathepsin A (acid carboxypeptidase)/neutral deamidase/esterase on a subset of bioactive peptides, including tachykinins and endothelin-1 [77-79], suggesting its contribution to a variety of intracellular and extracellular cell processes [80,81]. As for the protective

functions of CTSA, it forms a multienzyme complex with lysosomal neuraminidase 1 (EC 3.2.1.18; NEU1) and acid β-galactosidase (EC 3.2.1.23; GLB1) to activate NEU1 and protect GLB1 from physiological proteolysis [70,75] The association of NEU1 with CTSA, which probably serves as a molecular chaperone, is particularly crucial for NEU1 neuramindase activity, since the activity is lost in the absence of CTSA, even though GLB1 retains at least 10–15% of the normal enzymatic activity levels [70,75]. The presence of combined deficiency of these enzymes and the excessive accumulation of sialyloligosaccharides derived from glycoproteins reveal the importance and contribution of the multienzyme complex to the physiological degradation of the N- and O-glycans derived from glycoproteins.

5. Disorders of glycoprotein carbohydrates and therapeutic approach

5.1. Lysosomal storage diseases (LSDs) causing metabolic errors of glycoprotein catabolism

Lysosomal storage diseases (LSDs) are inherited metabolic disorders caused by genetic defects in the lysosomal enzymes and their cofactors. LSDs result in the excessive accumulation in lysosomes of undegraded substrates, including oligosaccharides derived from glycoproteins, glycosphingolipids, and glycosaminoglycans derived from proteoglycans [66,81]. LSDs comprise more than 40 different disorders, and each incidence is about 1 per 100 thousand births, with differences among disorders and races. The clinical manifestations of LSDs are quite heterogeneous, but many of them involve neurological disorders.

LSDs that are associated with the accumulation of oligosaccharides derived from glycoproteins include α-mannosidosis [82-84], β-mannosidosis [82,83], fucosidosis [82-84], sialidosis [82,85-87], galactosialidosis [70,75], etc. (Table 1). In this chapter, we will focus on sialidosis and galactosialidosis, both of which are associated with NEU1 deficiency and characterized by the accumulation of sialylololigosaccharides and lead to heterogeneous clinical manifestations.

Diseases	Responsible enzymes	Responsible genes	References
Fucosidosis	α-Fucosidase	FUCA1	[82,83]
α-Mannosidosis	α-Mannosidase	MAN2B1	[82,83]
β-Mannosidosis	β-Mannosidase	MANBA	[82,83]
Sialidosis	Lysosomal sialidase (Neuraminidase 1)	NEU1	[82,85-87]
Galactosialidosis	Protective protein/cathepsinA[*]	CTSA	[70,75,85,88]
Aspartylglucosaminuria	Aspartylglucosaminidase	AGA	[66]
Schindler disease / Kanzaki disease	α-N-Acetylgalactosaminidase	NAGA	[66]

Table 1. Lysosomal storage diseases (LSDs) caused by the defect in glycoprotein catabolism. *The defect of protective protein/cathepsin A causes the combined deficiencies of lysosomal sialidase (NEU1) and acid β-galacosidase (GLB1).

5.1.1. Sialidosis (MIM 256550)

Sialidosis is an autosomal recessive, lysosomal neuraminidase 1 (*NEU1*; 6p21) deficiency [82,89]. NEU1 normally cleaves terminal $\alpha 2 \rightarrow 3$ and $\alpha 2 \rightarrow 6$ sialyl linkages of several oligo-saccharides and glycopeptides and was found increased in tissues and fluids of affected patients. A 1.9-kb cDNA containing an open reading frame of 1,245 nucleotides in size is predicted to code for a protein that is 415 amino acids long. Distinct from other human neuraminidases (including cytoplasmic NEU2, plasma membrane NEU3, and mitochondrial/lysosomal NEU4), NEU1 needs to form a complex with CTSA and GLB1 to be catalytically active, as described above [70,75]. Type I sialidosis, the milder form, is characterized by the development of ocular cherry-red spots and generalized myoclonus in the second or third decade of life. Additional manifestations, reported in more than 50% of patients, include seizures, hyperreflexia, and ataxia [86,87]. Type II sialidosis is distinguished from the Type I milder form by the early onset of a progressive, rather severe [82,86,87] mucopolysaccharidosis-like phenotype with visceromegaly, dysostosis multiplex, and mental retardation. It has also been suggested that the residual NEU1 activities in the affected patients in relation to the kinds of identified missense mutations may be responsible for determining the clinical phenotypes (milder Type I and severe Type II) of the patients [82,86,87].

5.1.2. Galactosialidosis (MIM 256540)

Galactosialidosis is an autosomal recessive deficiency in the *lysosomal protective protein/cathepsin A* gene (*CTSA*; 20q13.2) [75,85]. This disorder is characterized by combined deficiency of its acid carboxypeptidase/neutral deamidase as well as GLB1 and NEU1, due to the defect of multienzyme complex formation. Multiple deficiencies arise because CTSA needs to physiologically associate with NEU1 and GLB1 and form a high-molecular-weight multienzyme complex to activate NEU1 and protect GLB1 from proteolytic degradation, as described above [70,85,88]. All patients exhibit clinical manifestations that are typical of a lysosomal disorder, such as coarse facies, cherry-red spots, vertebral changes, foam cells in the bone marrow, and vacuolated lymphocytes. Three phenotypic subtypes have been recognized. First, the early infantile form is associated with fetal hydrops, edema, ascites, visceromegaly, skeletal dysplasia, and early death. Second, the late infantile type is characterized by hepatosplenomegaly, growth retardation, cardiac involvement, and rare occurrence of neurologic signs. Third, the juvenile/adult form is characterized by myoclonus, ataxia, angiokeratoma, mental retardation, neurologic deterioration, absence of visceromegaly, and long survival. The majority of patients belonging to the juvenile/adult group was reported Japanese origin.

5.1.3. Molecular therapy for LSDs

Several therapeutic approaches have been developed and clinically applied to LSDs [90], including bone marrow transplantation (BMT), enzyme replacement therapy (ERT), gene therapy (GT), and substrate reduction therapy (SRT). BMT, ERT, and *ex vivo* GT utilize

hematopoietic cells transduced with the cDNA of human lysosomal enzymes, which is based on the findings that normal lysosomal enzymes secreted from the donor cells or exogenously administered can be endocytosed via glycan receptors. These receptors include mannose receptors that recognize terminal mannose residues [91] and CI-M6PR [74], as described above, that are delivered to the lysosomes where the captured enzymes can exhibit their normal catabolic functions (cross-correction). However, BMT and *ex vivo* GT have several disadvantages, including high morbidity and mortality, as well as incomplete responses to therapy depending on the clinical phenotypes. On the other hand, the intravenous ERT utilizes recombinant human lysosomal enzymes produced by mammalian cell lines (Chinese hamster ovary (CHO) and human HT1080) stably expressing their cDNA and has been found to be the most effective treatment for several LSDs involving visceral symptoms, including type 1 Gaucher disease [92], mucopolysaccharidosis (MPS) type I [93], type II [94], and type VI [95], Fabry [96], and Pompe diseases [97]. However, the intravenous ERT also has several disadvantages including long-term therapy, production of neutralizing antibodies [98], high cost, and little effectiveness to LSDs involving central nervous system (CNS) symptoms due to the blood-brain barrier (BBB). Clinical trials of the intrathecal ERT are being carried out for treating MPS type I [99], II, and IIIB.

GT has advantages such as a long-lasting treatment with a single administration utilizing recombinant viral gene transfer vectors, [100-103] including retrovirus, adenovirus, herpes simplex virus, adeno-associated virus (AAV), and lentiviruses, albeit with its own attendant concerns, such as low levels and persistence of expression, as well as insertional mutagenesis resulting in neoplasia.

Alternatively, SRT based on prevention of the biosynthesis of natural substrates by utilizing synthetic substrate analogs, has been clinically applied [90,104,105], even though its utility is limited by side effects, continuous administration, and high cost.

In contrast, no definitive treatment is clinically available for LSDs involving glycoprotein catabolism, even though preclinical experiments with animal models have been performed. Heterologous BMT in a ferine α-mannosidosis model caused by a 4-bp deletion in the feline *MAN2B1* gene showed significant therapeutic effects on the CNS symptoms, in which case the therapy began when mild clinical signs were present [106]. Brain-directed GT using the AAV vector for 8-week-old cats with α-mannosidosis also showed remarkable restoration of brain α-mannosidase activity, improvement in myelination abnormalities, reduction of substrates in the neurons, neurological signs, and prolonged life span [107]. A canine α-fucosidosis model caused by a 14-bp deletion in the canine *FUCA1* gene has also been treated with heterologous BMT, the administration of which at an early age demonstrated efficacy for CNS symptoms [108].

Moreover, a murine galactosialidosis model (*Ctsa-/-*) was treated with cell-type specific *ex vivo* GT [109,110] by using donor bone marrow-derived cells that were transduced with murine-based retroviral vectors, containing human CTSA cDNA under the control of the promoter of murine monocyte/macrophage-specific colony-stimulating factor-1 receptor. Transgenic macrophages infiltrated and resided in all organs, and correction due to the secreted CTSA was observed not only in hematopoietic tissues but also in nonhematopoietic

organs, including the CNS. Systemic GT for *Ctsa-/-* mice was also performed using a liver-tropic recombinant AAV-2/8 vector [111]. Despite the restricted expression of CTSA in the liver, dose-dependent and widespread correction of the disease phenotype in other systemic organs, serum, and urine, was observed, suggesting the protein-mediated mechanism of cross-correction.

Several approaches used to develop ERT for sialidosis and galactosialidosis have been challenged. The murine sialidosis model was treated with a short-term, high-dose ERT using baculovirus-derived recombinant *Neu1* [112]. The terminal mannosylated Neu1 taken up by resident macrophages in visceral organs restored the Neu1 activity and reduced the accumulation of sialyl substrates in lysosomes; however, mice developed a severe immune response towards the exogenous Neu1 as a side effect [112]. Recently, Itoh *et al* succeeded in producing a transgenic silkworm strain that overexpresses mature human CTSA in the middle silk glands (unpublished data). Purified mature CTSA carrying the human-like, high-mannose-type oligosaccharides lacking insect-specific carbohydrate moiety was taken up by murine monocytic cell lines via MR to be delivered to lysosomes. The conjugate between CTSA and a cell-penetrating peptide was also efficiently incorporated into the fibroblasts derived from galactosialidosis patients to be delivered to lysosomes and thereafter reduced the accumulation of sialyloligosaccharides in the cells. The novel recombinant human CTSA could be applied as a low-antigenic enzyme to intrathecal ERT for treating galactosialidosis patients exhibiting neurological symptoms.

6. Conclusions

Carbohydrates are very important molecules not only as energy sources but also for a wide variety of cellular functions, ranging from cell-cell interaction to immunity (1). Examples of glycosylation disorders described above clearly demonstrate that addition of carbohydrates to proteins is crucial for maintaining normal cellular physiology and that glycosylation disorders affect various cellular activities. The sugar chains, although not the direct gene products, contain essential information for the proper cellular function. The information, encoded by carbohydrate structures, is regarded as the sugar codes and is deciphered by a collection of carbohydrate-recognizing molecules, such as selectins and galectins [113,114]. In other words, glycosylation disorders can be considered as failures in interpreting the sugar codes. Due to their structural similarity and heterogeneity, carbohydrates are the most difficult molecules to study with the methods commonly used for nucleic acids and proteins. While the structure-function relationship of carbohydrates have remained unclear for a long time, the recent progress in separation, mass spectrometry, and genome-wide association studies of carbohydrates has been bringing information more rapidly than ever[115,116]. We expect that rapidly increasing knowledge of glycan structures and functions will help not only understand the importance of glycosylation in biology and diseases but also, in the near future, exploit the way to treat glycosylation-related diseases.

Acknowledgements

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